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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,904	01/23/1998	HARRY MEADE	TCI-028DV	2693

31904 7590 04/20/2005

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/012,904	MEADE ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/8/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21,25-27 and 29-35* is/are pending in the application.

4a) Of the above claim(s) *31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21,25-27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 19, 21, 25-27, 29-35 are pending in the application.

This Office Action is in response to the Amendment filed on 2/8/05.

Response to Amendment

The examiner acknowledges that claim 23 was cancelled by amendment filed on 3/10/04, and it was inadvertently included in the 103 rejection mailed on 6/16/04. The rejection is thus moot in view of the cancellation of the claim.

The rejection to claims 29-30 under 35 U.S.C. 112 1st paragraph (written description) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 29 and 30 under 35 U.S.C.103 (a) has been withdrawn in light of the new grounds of rejection (112 1st and 2nd) necessitated by Applicant's amendment.

The rejection of claims 19, 21, 25-27 under 35 U.S.C.103(a) is maintained for reasons set forth of the record mailed on 6/16/04 and further discussed below.

Claims 19, 21, 25-27, 29 and 30 are rejected under 35 U.S.C. 112 1st paragraph (new matter) for reasons discussed below.

Claims 19, 21, 25-27, 29 and 30 are rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Claims 31-35 are withdrawn from consideration for being directed for non-elected subject matter (see reasons below).

Response to Arguments

Claims 19 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97).

In response to this rejection, Applicants argue that the amendment of the claims bring the invention further away from the teaching of prior art citations Meade et al. and De Boer et al. Applicants argue that the examiner has not established the prima facie case of obviousness for reasons discussed previously. Applicants further assert that there is no requirement in patent law that a patentable product be produced by non-obvious or novel methods, regardless of whether the product is a DNA, or an amino acid sequence but only that the product itself be non-obvious according to *In re Bell* and *In re Thorpe*. Applicants draw the analogy of *In re Bell* with the instant invention in which the genes for human insulin growth like factors I and II (IGF) were not rendered obvious by the previously disclosed full amino acid sequence. Applicants reiterate that the claimed invention is not obvious because there is no motivation to combine the cited references according to Carela v. Starlight Archery, Pro-Mold & Tool Co., Inc. v. Great Lake Plastics, Inc., Ashland Oil Inc., v. Delta Resins & Refractories, Inc., and Northern Telecom Inc., v. Datapoint Corp.

Applicants further argue that Meade et al. fails to teach: I. expressing light chain and heavy chain of the immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors; II. a separate construct for the light chain and the heavy chain for the production of a single immunoglobulin; III. use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk; IV a unique restriction

site between promoter and the 3' non-coding sequence, wherein the immunoglobulin sequence is inserted into the restriction site; the advantage of having the unique restriction site for easy modification of the vector, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art.

Applicants further argue that DeBoer et al. fails to teach these deficiencies. Applicants assert that even Deboer et al. (col. 30 lines 45-50 and Figure 7E) provides for the development of a construct having a casein promoter and a 3' non-coding sequence, and unique restriction sites including XhoI, between the promoter and the 3' coding sequence, however, neither textual citation of DeBoer or the Figure cited in the previous office action demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted. Applicants thus conclude that this citation simply does not present the elements of the current invention regarding the production fully functional, fully assembled immunoglobulin in transgenic mammalian milk. It also fails to teach such modification of the prior art or any combination with Meade et al. Applicants thus conclude that the claimed invention is not obvious in view of Meade or Deboer alone or in combination.

The above arguments has been fully considered but deemed unpersuasive. The claimed invention is obvious in view of the combined teaching of Meade et al. and DeBoer et al. for reasons discussed in detail in the previous office actions. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either

in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since Meade et al. already teach a construct for expressing heterologous proteins including immunoglobulin (see col.3, lines 38-39) in mammalian milk, addition of a unique restriction site in between promoter and 3' non-coding region for addition of sequence encoding protein such as disclosed by DeBoer et al. is routine experimentation in the field of molecular cloning. One of ordinary skill in the art would have been motivated to provide such modified vectors to obviate any undesirable cleavage of the cDNA inserts which intrinsically contain common restriction endonuclease recognition sites. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as tissue specific expression, and ease of insertion of various cDNAs of interest, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA constructs to obtain a DNA construct with tissue specificity, and a site for insertion of a desired cDNA into the vector without undue experimentation barring evidence to the contrary. Therefore, the claimed invention would have been obvious to one of ordinary skill of art at the time the invention was made.

In response to Applicant's argument with regard to *In re Bell*, the examiner fails to see the relevance of the decision of *In re Bell*, *In re Thorpe* and the 103 rejection to the instant claims. While the decision of *In re Bell* assert that the genes for human insulin growth like factors I and II (IGF) were not rendered obvious by the previously disclosed full amino acid sequence, the instant rejection is not based on any amino acid sequence of the immunoglobulin

protein. The decision of *In re Thorpe* deals with the patentability of product by process claims. Contrary to Applicant's assertion, the rejection is not based on the requirement to produce the claimed product by non-obvious method. The combined teaching of Meade and Deboer renders the instant claimed construct obvious because it teaches every element of the instantly claimed DNA construct and provide sufficient motivation to combine these teachings (see discussion in the previous office actions and above).

The alleged deficiencies of I-III are not limitations of claims 19, 21 and 25-27. The amended claim 19 read on a DNA construct that comprises a promoter sequence, an immunoglobulin coding sequence, a 3' non-coding sequence and a unique restriction site between the promoter and the 3' non-coding sequence, the recitation of "wherein each coding region may be expressed individually" does not impart a structural difference to the claimed vector and the one taught by the prior art. Absent evidence from the contrary, the immunoglobulin coding region taught in the cited reference can also be expressed individually. (Note, since it is unclear whether the construct comprises both heavy chain and light chain, or only one of those (see 112 2nd rejection below), this rejection is based on the claim interpretation of a construct comprises either a light chain or a heavy chain). Contrary to Applicants' assertion that DeBoer et al. do not teach a unique restriction site in between a mammary gland promoter and 3' non-coding sequence, DeBoer et al. indeed teach such limitation. In response to Applicant's assertion that neither textual citation of DeBoer or the Figure cited in the previous office action demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted, Applicants is reminded to read carefully of the cited text (Col.30, lines 45-50) and

the figure (Figure 7E), the restriction site Xho I clearly lies in between the bovine αS1 casein promoter (a mammary gland specific promoter) and the 3' non-coding region. Unless Applicants can provide reason why an immunoglobulin coding sequence cannot be inserted into this site, this reference apparently teaches the limitation of "the unique restriction site between the promoter and 3' non-coding region," the supposedly advantage of the instant invention over prior art.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97, effective filing date of 11/27/90) as applied to claims 19 and 25-27 above, and further in view of Bischoff et al. (FEBS Letters, 305:265-268, 1992), Buhler et al. (Bio/Technology, 9: 835-838, 1991), Gordon et al. (Bio/Technology, 5: 1183-1187, 1987), Ebert et al. (Bio/Technology, 8: 140-143, 1990), and Stinnakre et al. (FEBS Letters, 284:19-22, 1991).

Applicants did not provide any argument with regard to this rejection. Therefore, this rejection is maintained for same reason as set forth in the previous office actions.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 21, 25-27, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claim 19 recites the limitation of "wherein each coding region may be expressed individually and wherein said immunoglobulin protein-coding sequence encodes a heavy chain coding region; wherein said immunoglobulin protein-coding sequence encodes a light chain coding region." Claim 29 is drawn to a mammary gland epithelial cell comprising two constructs, wherein one constructs is the construct of claim 19, and the other one comprises "immunoglobulin protein coding sequence which encodes both a light chain and a heavy chain...wherein the cell expresses light and heavy chain separately." However, the specification as originally filed does not teach a DNA construct encoding a heterologous immunoglobulin comprising both heavy chain coding region and light chain coding region in the same construct which can be expressed individually. Therefore, such recitation constitutes new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 21, 25-27, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 19, 21, 25-27, 29 and 30, the recitation of "wherein the immunoglobulin protein coding sequence encodes a heavy chain coding region; wherein said immunoglobulin protein coding sequence encodes a light chain coding region" renders the

claims indefinite because it is unclear whether the construct encodes both heavy chain and light chain or just one of them. As such, the metes and bounds of the claim cannot be established.

Regarding claim 30, the recitation of "the construct of claim 19 further comprising, wherein the cell expresses the light chain and heavy chains separately and the sequence so expressed are fully human sequences" renders the claim indefinite because it is unclear what the construct further comprises besides what is disclosed in claim 19. As such, the metes and bounds of the claim cannot be established.

Election/Restrictions

Newly submitted claims 31-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant elected the invention of Group II for examination in the response filed on 7/27/1999, which is directed to a DNA construct encoding a heterologous immunoglobulin. Claims 31-35 are drawn to a non-human transgenic mammal comprising the insertion of two separate DNA constructs into the genome of said mammal, which does not belong to the elected subject matter. The DNA construct and the transgenic mammal are patentably distinct because they are drawn to compositions that are chemically, biologically and functionally distinct from each other. The DNA construct is not necessarily used in producing the transgenic mammal, it can also be used to express immunoglobulin *in vitro*. A search of one group is not co-extensive with the search of another, and a search of both group would have been burdensome. As such, newly added claims 31-35 do not belong to the invention of Group II as originally elected by Applicants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claims 31-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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